IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	ANDERSON, ET AL.
Serial No.	:	904,662
Filed:	:	SEPTEMBER 8, 1992
For	:	GENE THERAPY
Group	:	1804
Examiner	:	JACQUELINE STONE

Honorable Commissioner of Patents
Washington, D.C. 20231

SIR:

W. French Anderson declares as follows:

1. He is one of the inventors of the referenced application.

2. He has attached hereto as Exhibit 1 a list of human gene therapy protocols, and to the best of his information and belief, the protocols listed as 1-38 have been approved by the Recombinant DNA Advisory Committee (RAC), a committee of the National Institutes of Health. All of such protocols (except for protocols No. 1-4, which are the protocols of the present application) were approved by the RAC after the above-named inventors had demonstrated the feasibility of human gene therapy through the ADA protocol of the present application.

3. To the best of his information and belief, RAC approval of the human gene therapy protocols 5-38 was obtained in a time period, which on the average was six months or less whereas it took over 3 years to obtain RAC approval for Anderson's initial gene therapy protocol (protocol 1, the ADA protocol of this application): April 24, 1987 (the date of the original pre-protocol submission to the Human Gene Therapy Subcommittee of the RAC)

to July 31, 1990. Now, most protocols are approved after an approximately eight week RAC review.

4. The approved protocols 5-38 are directed to human gene therapy with a variety of DNA sequences, employing a variety of delivery vehicles, and are directed to both ex vivo and in situ (in vivo) transduction of human cells. Thus, for example, such protocols include the following:

1. TNF, which is a secreted cytokine
2. IL-2, a secreted lymphokine;
3. LDL receptor, a membrane protein;
4. TK, an activatable viral gene;
5. HLA-B7, a cell surface antigen;
6. HIV-gp120, a surface antigen;
7. IL-4, a cytokine;
8. antisense-RAS, an antisense molecule to an oncogene;
9. p53, a tumor suppressor gene;
10. CF, an integral membrane transport protein;
11. GM-CSF, a hematopoietic colony-stimulating factor;
12. gamma interferon, a cytokine;
13. MDR, a membrane transport protein;
14. glucocerebrosidase, an intracellular enzyme;
15. mutated HIV, a viral protein;
16. Rev, a viral transcription factor;
17. anti-IGF-1, an antisense molecule to a cell growth factor; and
18. ribozyme, an RNA-cleaving RNA molecule.

In addition, the RAC-approved protocols encompass a wide variety of delivery means, such as retroviral vectors, adenovirus vectors, liposomes for delivery of plasmid DNA, and viral-producer cells.

In addition, such RAC-approved protocols encompass both ex-vivo transduction and in situ (in vivo) transduction of cells. Thus, for example, the TK protocol involves the use of a producer cell, which transduces cells in vivo.

The 5 CF protocols involve intratracheal or intranasal infusion of an adenovirus vector for transduction of cells in vivo.

In addition, such RAC-approved protocols include a protocol for direct injection into a cancer mass for transduction of cells in vivo.

5. To the best of his information and belief, the RAC does not approve a human gene therapy protocol unless there is a reasonable expectation of efficacy. In his opinion, the rapid approval of the human gene therapy protocols 5-38, in large part, resulted from the fact that the inventors of the present application had demonstrated the feasibility of human gene therapy through protocol 1, the ADA protocol of the present application. In particular, the demonstration of the feasibility of human gene therapy through the ADA protocol indicated that concerns, such as those raised by the Examiner on page 3 of the Office Action in the present application, with respect to the inappropriateness of human gene therapy, had been obviated, whereby it was now possible for those skilled in the art to design and obtain RAC approval for a wide variety of human gene therapy protocols.

6. Prior to the inventors demonstration of the feasibility of human gene therapy, there were no approved human gene therapy protocols. After such demonstration of the feasibility of human gene therapy, in a period of less than three years, there exists 37 additional approved human gene therapy protocols in the United States. In his opinion, the design and approval of such human gene therapy protocols was enabled by the inventors demonstration that human gene therapy is feasible.

7. He has attached hereto as Exhibit 2 a summary of the Institutions involved with human gene therapy protocols.

8. He has attached hereto as Exhibit 3 a graph which indicates the cumulative number of patients through the early part of 1993 who have received gene therapy. The first point on the therapy curve is the first patient on the ADA protocol of the present application. The graph of Exhibit 3 is incomplete in that it covers only to May 1, 1993. The graph illustrates the significant increase in human gene therapy patients, and the rapidity of such increase, after the inventors demonstrated the feasibility of human gene therapy.

9. He declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

W. French Anderson

W. FRENCH ANDERSON

Dated: October 15, 1993

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